Original Article

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The Effect of Changes in the Visual Experience during Critical Periods of Brain Development on the Synaptic Plasticity of Hippocampal CA1 Neurons in Rats

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ABSTRACT

BACKGROUND AND OBJECTIVE: Changes in the visual experience during the critical periods of brain development lead to the dysfunction of the visual cortex.The visual cortex is a major supplier of sensory input in the mammalian hippocampus. This study aimed to investigate the effects of visual deprivation on the synaptic plasticity of CA1 neurons in this area.

METHODS: This experimental study was conducted on 48 male Wistar rats who had been classified into the two main groups of a 12-12 Light Reared (LR) and Dark Reared (DR) since birth.To perform the experiments, the rats were categorized under 3 subgroups of 2, 4 and 6 weeks of age. Excitatory postsynaptic potentials (EPSP) were recorded for 30 minutes from the dendrites of neurons in the CA1 area. Afterwards, long-term potentiation (LTP) was induced through Tetanic stimulation. Finally, the amplitude of the responses were measured before and after the Tetanic stimulation.

FINDINGS: The amplitude of basic responses in the 2WLR and 6WLR group were 1.28±0.05 Mv and 1.09±0.03 Mv, respectively ($p<0.0001$) while the range increased from 1.30±0.30 Mv in the 2WDR group to 1.50±0.4 Mv in the 6WDR group ($p<0.0001$). Upon LTP induction, the highest rise in the amplitude response was observed at the age of 2 weeks in the animals. However, the increasing responses in both groups of LR and DR diminished with age ($p<0.0001$).

CONCLUSION: Visual deprivation during the critical periods of brain development might lead to an increase in the basal synaptic activity of hippocampal CA1 neurons through an age-related process. Although it does not interrupt the induction of LTP in neurons, it might reduce its intensity and stability.

KEY WORDS: Visual Experience, Synaptic Plasticity, Hippocampus, Critical Period, Wistar Rats.

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Introduction

Critical period of mammalian brain developmentis a period which starts atbirth and lasts until the maturation of synaptic circuits of the central nervous system. The formation of synaptic circuits during this period is affected by two major physiological procedures: the intrinsic activity of neuronsas a result ofgenetic activity and the interaction with the environment through environmental signals (1). This period takes about 6 weeks in rats' brain (2). The visual system is the most significant sensory input to the mammalian brain. Thus, the signals received by this system play a pivotal role inthe maturation of the brain circuits (3). The developmental role of these signals in the critical periodhas been surveyed in several studies (4,5). In addition, different studies have indicated that changes in these signals dramatically impact on the development of the brain cortex (6-8). A majority of studies have investigated the effects of visual signalson the visual cortex (9,10).

For instance, Goel et al. suggested that visual deprivation during the critical periods of brain development, even for as long as two days, could lead to the impairment of synaptic activity in the visual cortex of rats' brain (11). Hippocampus is a part of the brain's limbic system which is located deeply in the temporal lobe influencing the process of learning and memory (12). It has proven that all the sensory corticesare responsible for sending a part of their signals to this structure which results in the formation of learning and memory after processing of the information (13). Thus, it could be inferred that learning and memory formation in the neural circuits are followed by thechanges in the activity of synaptic connections (14). Long-term potentiation (LTP) is a well-known physiological process which is induced through induction of the high-frequency stimulation to the neuralcircuits and it is considered as a plausible laboratory model for changing synaptic activity, also known assynaptic plasticity (15).

Containing organized neural circuits, the hippocampal structures, especially the CA1 area, are a proper reference for investigating this process (16). Moreover, a critical period of development is known to occurfor the hippocampus which is similar to that of the sensory cortices. It has been suggested that certain environmental changes such as sensory deprivation (17), living in crowded environments andan increase in the sensory inputs to the brain (18), could bring about changes in the performance of its neurons. Given the fact that part of the visual signalsenter the hippocampal formation and that transformed visualsignals could bring about changes in the structure and function of the visual cortex,it is probable that modified visual messages could also affect the structure and function of the hippocampus during the critical period of brain development.

Therefore, this study aimed to investigate the impact of different periods of visual deprivation during the critical period of brain development on the synaptic plasticity of the hippocampal CA1 area in rats.

Methods

This experimental study was conducted on 48 male Wistar rats. Animals were kept in the standard animal house and sufficient access to water and food. Protocol of the experiments was reviewed and approved by the Ethical Committee of Kashan University of Medical Sciences. With regards to the light conditions, the animals were divided into two main groups of Light Reared (LR) and Dark Reared (DR). The LR animals had been preserved under normal light conditions (i.e 12 hours of light and 12 hours of dark) while the DR ratshad been preserved in complete darkness from birth to the end of the experiment. Moreover, each of the main groups were divided into3 subgroups (N=8). The first subgroup included rats of 2 weeks of age (2WLR, 2WDR), the second included rats of4 weeks of age (4WLR, 4WDR) and the third subgroup included rats of 6 weeks of age (6WLR, 6WDR). Half an hour before the beginning of the tests, the ratswere transferred to the laboratory where they were anesthetized by an intraperitoneal injectionof Urethane (1.5g per kg of body weight).

The animals in the DR group were initially anesthetized by drugs in the darkroom and their eyes were shut tightly upon whichthey entered the laboratory. After fixating their head in a Stereotaxic apparatus (Stoelting USA), 0.5 ml of 1% lidocaine was injected under their head skin in addition to local anesthesia so that the scalp would be removed from the skullby an easy cut. Following that, the scalp was removed from the back of the neck to the vicinity of the nosewhile all other tissues were completely pushed in order for the skull to appear. After determining the Bregma, Lambda and midline on the scalp, the locations of electrods were highlighted by Stereotoxic Atlas (Paxinos and Watson) (19). The stimulating electrode

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was located on the axon of the Schaffer's collaterals of CA3 neurons at the coordinates of D=2.4 mm, LR=3.8 mm, AP=-4.2 mmand the recording electrode was located on the dendrites of CA1 neuronsat the coordinates of D=2.5 mm, LR=2.5 mm, AP=-3.4 mm. The electrodes were both Bipolar, Teflon-coated and made of stainless steel with a diameter of 0.005 inches (AM Systems USA).

The correct location of the electrodes was detected via Electrophysiological recording. To make sure, the accuracy of the palce of electrodes was examined by applying paired pulse. The 20% increase of the amplitude of the second response compared to the first one was indicative of the correct placement of the stimulating and recording electrodes. In response to the stimulation of the Schaffer's collaterals, the EPSPs were recorded, and amplified 2000x by an amplifier (WSI, A3308).

Then, they were given to the Data Acquisition Board (AD Instruments, Australia) where they were converted into digital data and recorded. About 30 minutesafter the first recording of the responses and the timewhen the amplitude responsesremained unchanged with the steady intensity of the stimulation, the Input/Output curve was drawn. The electrical stimulation intensity in which 60% of the maximum amplitude of the response was obtained was selected as the stimulation intensity for the continuation of the trial as well asthe tetanicstimulation.

Furthermore, stimulations at a frequency of 0.1Hz were applied for 100 mswith adelay of 5 ms.Afterwards, EPSPs were recorded for 30 minutes. In order to induce the LTP on the tested neuronal circuits, High Frequency Stimulation (HFS) was applied. The stimulation pattern consisted of 10 trains including ten 200Hz stimulation frequencieswith an interval of 2ms. The duration of each stimulating pulse was 0.1ms. After the induction of tetanic stimulation, the process of stimulation and recording continued for 2 hours. The Scope for Windows software (Australia, PowerLab) was used for measuring the stimulation and recording as well as the analysis of the responses.

In order to compare the two groups, the percentage of changes in the amplitude responses were evaluated in mV before and after the tetanic stimulation. Any increase by 20% in the amplitude of the responsesthe tetanic stimulation was considered as an LTP induction criterion (20). The collected data were analyzed by One-way ANOVA and Tukey's post-analysis and $p<0.05$ was considered significant.

Findings

The test results revealed asignificant difference between the amplitude of all groups in the basic responsesas well as before and after the LTP induction. Moreover, the analysis of data on the responses recorded in the CA1 region of the rats' hippocampus in the LR group showedthe mean amplitude of the responses in the 2WLR group to be 1.28±0.05mV which decreased in the other two groupsas of 1.17±0.04 in the 4WLR group and 05.0±28.1 mVin the 2WLR group reaching 1.09±0.03 mV.

The results were also indicative of a significant difference in the amplitude responsebetween the groups of 2WLR and 4WLR (p=0.02) (fig 1).

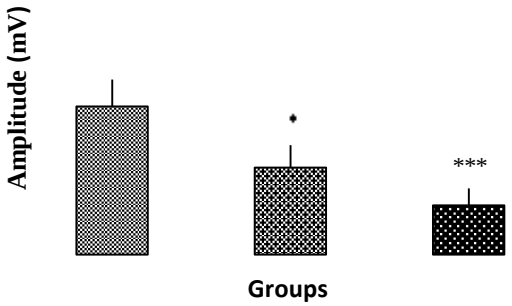


Figure 1. Comparison of of the mean amplitude resposes in different groups of animals grown in the natural light cycle of 12 hours (N=8 in each group)

The difference of amplitude between groups of 2WLR and 4WLR ($p<0.05$). The difference of amplitude between groups of 2WLR and 6WLR ($p<0.001$).

In addition, the difference of the amplitude responsewas found to be significant between the groups of 2WLR and 6WLR ($p<0.0001$). LTP induction leads to a significant increase in the amplitude of the fEPSP sandthe difference before and after the LTP induction was considered as significant in all the groups ($p<0.0001$). Along with aging and reaching the final maturation of the brain circuits, the increasing amplitude dropped after the Tetanicstimulation in all groups.

As a result, the maximum and the minimum increase were observed in the 2WLRand 6WLR rats, respectively (Figure 2). However, the difference between the amplitude responses after the LTP induction was considered as significant in all groups ($p<0.0001$).

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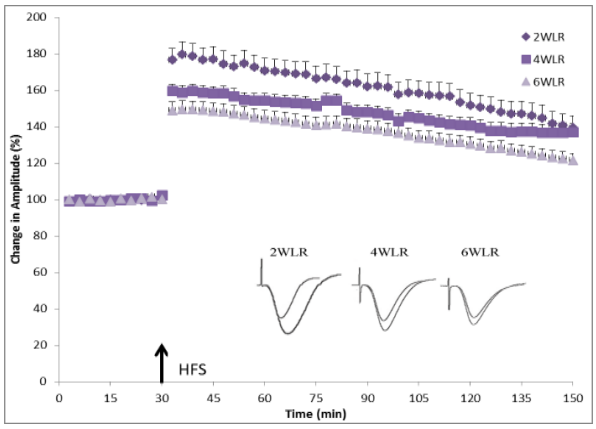


Figure 2. Tetanic stimulation in fEPSP as recorded in the hippocampal CA1 region of the rats in natural light-dark cycle induced by LTP.

The difference between the amplitude responses in all groups after LTP induction ($p<0.0001$)

The analysis of the data based on the amplitude responses of the animals grown in 24 hours of darkness indicated that with the age,the responses experienced an increasingtrend.The mean amplitude responses in the 2WDR group was1.30±0.03mV, while it reached 1.41±0.03 and 1.50±0.04mVin the next two groups, respectively.Furthermore, the results revealed a significant difference in the amplitude response between the groups of 2WDR, 4WDR and 6WDR ($p<0.0001$) (Figure 3). However, the difference in the basic amplitude response was not considered as significant between the two groups of 4WDR and 6WDR. For another thing, enhancing the responsesin all the three aforementioned groups after the LTP induction was higher than 20% as recorded during 2 entire hours. amplitude after applying high frequency stimulation in the perforant pathof the hippocampal CA1 of the animalsgrownin the 24 hours of darkness. However, the increase in the amplitude of all responses was lower after the LTP induction compared tothe same-agerats who were grown in the light. According to statistical analysis of the data, the difference before and after the LTP induction was found to be significant in all groups ($p<0.0001$). Furthermore, comparison of the data in thegroups of animals revealed thatwith age, the enhancement ofthe responses reduced (Figure 4).

Considering a criterion of 20% increase in the amplitude response after the induction of LTP, it could be inferred thatdespite the induction in the 6WDR group, it only lasted about half an hour. Statistical analysis of the results showed a significant difference between the amplitude response after LTP induction in 2WDR and 6WDR groups ($p<0.0001$) while the rest of the comparisons were not proven to be significant.

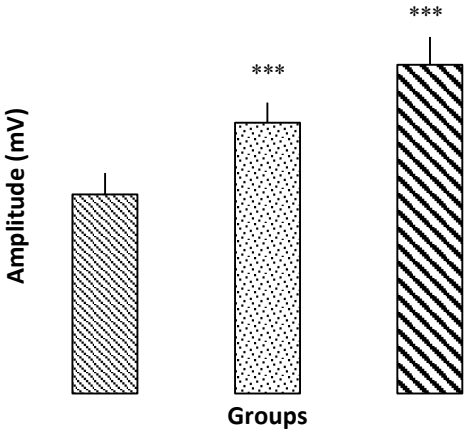


Figure 3. Comparison of the mean amplitude in different groups of animals grown in the darkness for 24 hours (N=8 in each group).

Differences in the amplitude responses between the groups of 2WDR, 4WDR and 6WDR ($p<0.0001$).

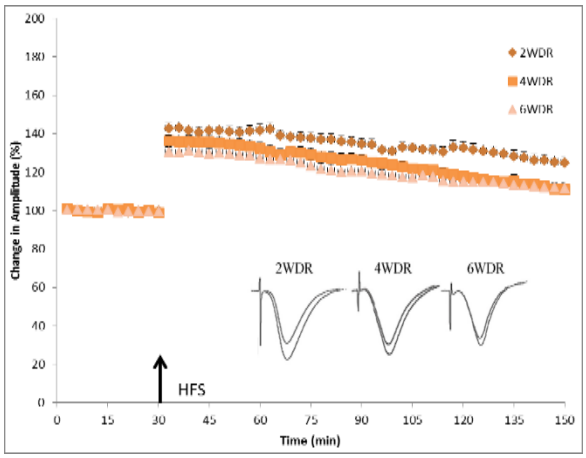


Figure 4. Following theTetanic stimulations in therecorded fEPSP of the hippocampal CA1 area of the rats grown in complete darkness,a significant increase was observed in the amplitude response and the induction of LTP in all the groups.

The difference between the amplitude response and LTP induction between the groups of 2WDR and 6WDR ($p<0.0001$).

Discussion

The results of the present study indicated that withageand approaching the end of the critical period of brain development, the extent of post-synaptic potentialsmight decrease in the hippocampal CA1while visual deprivation is likely to add to this rangethrough a

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time-dependent process. Moreover, the enhancement of field potentials is likely to diminish through an age-related process after a high-frequency stimulation of the circuits in this area. Although depriviation of the visual signals during this critical period did not seem to interruptthe induction of LTP in the circuits, it lead to a considerable decrease in the size and stability of synaptic response enhancement. Eckert et al. proved thatan increase in the environmental signals received by the brain during the critical period of development could result in the improvement of memory and LTP induction in the CA1 region of the rats' hippocampus through crowding the environment and after that (18). In another study, it was suggested thatcrowding the environment results in the enhancement of the basic responses as well as facilitating the LTP induction in the brain slices prepared from the rats' hippocampal CA1 area (21).

In their research, Talaei et al.proved thatchanges in the visual experience, even after puberty,could also impair the LTP induction in the rats' CA1 and dentate gyrus (22).What is the cause of the observed changes? In the answer, it could be stated that during the critical period of brain development the amount and type of various Neurotransmitter activities constantly change due to the intrinsic activity of the neurons and making contact with the environment in order to reach maturation and stability.Glutamate is the major excitatory neurotransmitter in the mammalian hippocampus (23) and GABA is the major inhibitory neurotransmitter(24).

Viaits two main receptors NMDA and AMPA, Glutamateis engaged in its activities. In the early stages of life, the only glutamatergic neurons expressed are NMDA receptors while other synaptic circuits and glutamate receptors are not expressed. These circuits are commonly referred toas AMPA Silent (25). Along with the development of the mammalian nervous system, AMPA receptors are also expressed in the glutamatergic circuits resulting in the maturation of the circuits. For instance, within 2 to 3 weeks after birth, almost half the glutamatergic hippocampal circuits exit the AMPA Silent mode (26). Thus, the expression of AMPA receptor subunits begin to increase in the rats' brain through an age-related process until their adolescence (27). In addition, it has been proven that visual deprivation could lead to an increased expression of the receptor subunits in the rats' visual cortex (28, 29). It has been established that in the early stages of life,the expression of NR2B, one of the receptor subunits of NMDA, is more abundant in the mammalian brain and along with the development of the brain,the expression of NR2A subunit gradually increases taking precedenceto the expression of NR2B during adolescence (30).

The switch between the two isoforms of NR2 subunit specifically requires the activity of the neuronal circuits as well as the sensory experience. In their research, Philpot et al.claimed that visual experience is vital to the evolutionary changes of the NMDA receptor subunits in the visual cortex (31). It has also been found that in animals deprived of seeing, the switching process does not occur and exposing them to light for only an hour is likely to ignite this process (32). With reference to the inhibitory neurotransmitter GABA, is has been confirmed that GABAergic neurons of the rats' hippocampuspractice stimulatory activities during the animals' infancy acquiring their inhibitory propertiesalong with the maturation of the nervous system (33).

Furthermore, it has been suggested that changes in the visual experience might alter the structure and function of GABAergic neurons in the visual cortex of rats (34, 35). From the findings of the current study it could be concluded thatchanges in the visual experience during the critical period of brain development occur through a time-dependent process. By altering thestimulatory and inhibitory neurotransmitters in the rats' brain,visual experience could increase thebasal synaptic transmission in the hippocampal CA1 neuronsof rats and although it does not interrupt the induction of LTP in neurons, it might reduce the intensity and stability of the induction.

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